

PATENT
Attorney Docket No. VACCINE-07971

AMENDMENTS TO THE CLAIMS

1-55 (canceled).

56. (currently amended) A method of making a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid and, if said heterologous antigen is determined to have an isoelectric point greater is greater than or equal to 7.0, adding and adding nucleotides that encode an acidic amino acid to said first nucleic acid to reduce said isoelectric point below 7.0;

combining said first and second nucleic acids, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop; and

expressing said first and second nucleic acids to produce a modified hepadnavirus core antigen comprising the amino acids encoded by said first and second nucleic acids.

57. (previously presented) The method of Claim 56, wherein in the absence of said adding nucleotides, expression of said modified hepadnavirus core antigen yields 25 fold or less particles than does expression of a wild type hepadnavirus core antigen.

58. (previously presented) The method of Claim 56, wherein after adding nucleotides to said first nucleic acid, said heterologous antigen encoded by said first nucleic acid is determined to have an isoelectric point in the range of 3.0 - 5.0.

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59. (previously presented) The method of Claim 56, wherein said adding nucleotides that encode an acidic amino acid results in a substitution of a non-acidic amino acid residue within said heterologous antigen, with said acidic amino acid residue.

60. (previously presented) The method of Claim 59, wherein said non-acidic amino acid residue is a basic amino acid residue.

61. (previously presented) The method of Claim 56, wherein said adding nucleotides that encode an acidic amino acid results in an insertion of said acidic amino acid residue.

62. (previously presented) The method of Claim 61, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid that flanks said heterologous antigen.

63. (previously presented) The method of Claim 62, wherein said acidic amino acid is a linker that flanks both sides of said heterologous antigen.

64. (previously presented) The method of Claim 56, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen.

65. (previously presented) The method of Claim 56, wherein said hepadnavirus core antigen comprises an artificial C-terminus.

66. (previously presented) The method of Claim 56, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen comprising an artificial C-terminus.

67. (previously presented) The method of Claim 56, wherein said hepadnavirus core antigen is a woodchuck hepadnavirus core antigen.

68. (previously presented) The method of Claim 56, wherein said hepadnavirus core antigen is a human hepadnavirus core antigen.

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69. (currently amended) A method of making a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid and, if said heterologous antigen is determined to have an isoelectric point greater is greater than or equal to 7.0, adding and adding nucleotides that encode an acidic amino acid to said second nucleic acid at a position within an immunodominant loop of said hepadnavirus core antigen or within an alpha-helix adjacent to said immunodominant loop;

combining said first and second nucleic acids, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop; and

expressing said first and second nucleic acids to produce a modified hepadnavirus core antigen comprising the amino acids encoded by said first and second nucleic acids.

70. (previously presented) The method of Claim 69, wherein in the absence of said adding nucleotides, expression of said modified hepadnavirus core antigen yields 25 fold or less particles than does expression of a wild type hepadnavirus core antigen.

71. (canceled).

72. (currently amended) The method of Claim 71, Claim 69, wherein said position is within said immunodominant loop of said hepadnavirus core antigen

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73. (currently amended) The method of Claim 71, Claim 69, wherein said position is within said alpha-helix adjacent to said immunodominant loop.

74. (currently amended) The method of Claim 71, Claim 69, wherein said adding nucleotides that encode an acidic amino acid results in a substitution of a non-acidic amino acid residue within said hepadnavirus core antigen, with said acidic amino acid residue.

75. (previously presented) The method of Claim 74, wherein said non-acidic amino acid residue is a basic amino acid residue.

76. (currently amended) The method of Claim 71, Claim 69, wherein said adding nucleotides that encode an acidic amino acid results in an insertion of said acidic amino acid residue.

77. (previously presented) The method of Claim 76, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid within said immunodominant loop of said hepadnavirus core antigen.

78. (previously presented) The method of Claim 76, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid within said alpha helix adjacent to said immunodominant loop.

79. (previously presented) The method of Claim 76, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid that flanks said heterologous antigen.

80. (previously presented) The method of Claim 79, wherein said acidic amino acid is a linker that flanks both sides of said heterologous antigen.

81. (currently amended) The method of Claim 71, Claim 69, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen.

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82. (currently amended) The method of Claim 71, Claim 69, wherein said hepadnavirus core antigen comprises an artificial C-terminus.

83. (currently amended) The method of Claim 71, Claim 69, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen comprising an artificial C-terminus.

84. (currently amended) The method of Claim 71, Claim 69, wherein said hepadnavirus core antigen is a woodchuck hepadnavirus core antigen.

85. (currently amended) The method of Claim 71, Claim 69, wherein said hepadnavirus core antigen is a human hepadnavirus core antigen.

86. (previously presented) The method of Claim 56, wherein said expression of said first and said second nucleic acids is in a bacterial cell.

87. (previously presented) The method of Claim 56, wherein said expression of said first and said second nucleic acids is in a mammalian cell.

88. (previously presented) The method of Claim 69, wherein said expression of said first and said second nucleic acids is in a bacterial cell.

89. (previously presented) The method of Claim 69, wherein said expression of said first and said second nucleic acids is in a mammalian cell.

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90. (currently amended) A method of making a nucleic acid that encodes a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid and, if said heterologous antigen is determined to have an isoelectric point greater is greater than or equal to 7.0, adding and adding nucleotides that encode an acidic amino acid to said first nucleic acid to reduce said isoelectric point below 7.0; and

combining said first and second nucleic acids so as to produce said nucleic acid that encodes said modified hepadnavirus core antigen, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop.

91. (previously presented) The method of Claim 90, wherein after adding nucleotides, said heterologous antigen is determined to have an isoelectric point in the range of 3.0 - 5.0.

92. (previously presented) The method of Claim 90, wherein said adding nucleotides that encode an acidic amino acid results in a substitution of a non-acidic amino acid residue within said heterologous antigen, with said acidic amino acid residue.

93. (previously presented) The method of Claim 90, wherein said non-acidic amino acid residue is a basic amino acid residue.

94. (previously presented) The method of Claim 90, wherein said adding nucleotides that encode an acidic amino acid results in an insertion of said acidic amino acid residue.

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95. (previously presented) The method of Claim 94, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid that flanks said heterologous antigen.

96. (previously presented) The method of Claim 95, wherein said acidic amino acid is a linker that flanks both sides of said heterologous antigen.

97. (previously presented) The method of Claim 90, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen.

98. (previously presented) The method of Claim 90, wherein said hepadnavirus core antigen comprises an artificial C-terminus.

99. (previously presented) The method of Claim 90, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen comprising an artificial C-terminus.

100. (previously presented) The method of Claim 90, wherein said hepadnavirus core antigen is a woodchuck hepadnavirus core antigen.

101. (previously presented) The method of Claim 90, wherein said hepadnavirus core antigen is a human hepadnavirus core antigen.

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102. (currently amended) A method of making a nucleic acid that encodes a modified hepadnavirus core antigen comprising:

providing a first nucleic acid encoding a heterologous antigen, wherein said heterologous antigen is 50 or fewer amino acids in length and has an isoelectric point greater than or equal to 7.0;

providing a second nucleic acid encoding a hepadnavirus core antigen, wherein said hepadnavirus core antigen is selected from the group consisting of a woodchuck hepadnavirus core antigen, a ground squirrel hepadnavirus core antigen and a human hepadnavirus core antigen;

determining that the isoelectric point of said heterologous antigen encoded by said first nucleic acid and, if said heterologous antigen is determined to have an isoelectric point greater is greater than or equal to 7.0, adding and adding nucleotides that encode an acidic amino acid to said second nucleic acid at a position within an immunodominant loop of said hepadnavirus core antigen or within an alpha-helix adjacent to said immunodominant loop; and

combining said first and second nucleic acids so as to produce said nucleic acid that encodes modified hepadnavirus core antigen, wherein said combining comprises placing said first and second nucleic acids in operable combination such that said heterologous antigen is expressable within said immunodominant loop or said alpha-helix adjacent to said immunodominant loop.

103. (canceled)

104. (previously presented) The method of Claim 102, wherein said position is within said immunodominant loop of said hepadnavirus core antigen

105. (previously presented) The method of Claim 102, wherein said position is within said alpha-helix adjacent to said immunodominant loop.

106. (previously presented) The method of Claim 102, wherein said adding nucleotides that encode an acidic amino acid results in a substitution of a non-acidic amino acid residue within said hepadnavirus core antigen, with said acidic amino acid residue.

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107. (previously presented) The method of Claim 106, wherein said non-acidic amino acid residue is a basic amino acid residue.

108. (previously presented) The method of Claim 102, wherein said adding nucleotides that encode an acidic amino acid results in an insertion of said acidic amino acid residue.

109. (previously presented) The method of Claim 108, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid within said immunodominant loop of said hepadnavirus core antigen.

110. (previously presented) The method of Claim 108, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid within said alpha helix adjacent to said immunodominant loop.

111. (previously presented) The method of Claim 108, wherein said adding nucleotides that encode an acidic amino acid results in at least one acidic amino acid that flanks said heterologous antigen.

112. (previously presented) The method of Claim 111, wherein said acidic amino acid is a linker that flanks both sides of said heterologous antigen.

113. (previously presented) The method of Claim 102, wherein said hepadnavirus core antigen is a truncated hepadnavirus core antigen.

114. (previously presented) The method of Claim 102, wherein said hepadnavirus core antigen comprises an artificial C-terminus.

115. (previously presented) The method of Claim 102, wherein said hepadnavirus core antigen is a woodchuck hepadnavirus core antigen.

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116. (previously presented) The method of Claim 102, wherein said hepadnavirus core antigen is a human hepadnavirus core antigen.

117. (new) The method of Claim 56, wherein said heterologous antigen is 26 or fewer amino acids in length.

118. (new) The method of Claim 56, wherein said heterologous antigen is less than 20 or fewer amino acids.

119. (new) The method of Claim 69, wherein said heterologous antigen is 26 or fewer amino acids in length.

120. (new) The method of Claim 69, wherein said heterologous antigen is 20 or fewer amino acids in length.

121. (new) The method of Claim 90, wherein said heterologous antigen is 26 or fewer amino acids in length.

122. (new) The method of Claim 90, wherein said heterologous antigen is 20 or fewer amino acids in length.

123. (new) The method of Claim 102, wherein said heterologous antigen is 26 or fewer amino acids in length.

124. (new) The method of Claim 102, wherein said heterologous antigen is 20 or fewer amino acids in length.